Brain & Development 41 (2019) 77–84

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Original article

Risk factors of cognitive impairment in pediatric epilepsy patients with focal cortical dysplasia

Nobusuke Kimura *, Yukitoshi Takahashi, Hideo Shigematsu, Katsumi Imai, Hiroko Ikeda, Hideyuki Ootani, Rumiko Takayama, Yukiko Mogami, Noriko Kimura, Koichi Baba, Kazumi Matsuda, Takayasu Tottori, Naotaka Usui, Satohiko Kondou, Yushi Inoue

National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, NHO, Shizuoka, Japan

Received 28 February 2018; received in revised form 10 May 2018; accepted 16 July 2018

Abstract

Objective: The purpose of this study was to identify the risk factors of cognitive impairment in pediatric epilepsy patients with focal cortical dysplasia (FCD).

Methods: 77 patients with histopathologically confirmed FCD were studied. The statistical relationship between cognition levels and clinical factors at presurgical evaluation was analyzed. Cognitive function was evaluated by development quotient or intelligence quotient (DQ-IQ).

Results: Ages at seizure onset were younger than 15 years (mean ± SD; 5.0 ± 4.2 years). Mean disease duration was 14.5 ± 8.5 years. Mean age at pre-surgical DQ-IQ evaluation was 34.8 ± 10.7 years. Mean DQ-IQ was 60.5 ± 20.5, and 41 of 77 (53.2%) patients had mental retardation (DQ-IQ < 70). Younger seizure onset and seizure clustering were significantly associated with lower DQ-IQ ($p < 0.001$). A multiple regression study identified higher seizure frequency pattern, a history of epileptic spasm and status epilepticus as aggravating factors of DQ-IQ decline ($R^2 = 0.63$, $p < 0.001$). On the other hand, the risk was decreased in patients with habitual focal aware seizure and transient seizure-free periods up to 6 months in the course of epilepsy. FCD location (FCD site, extent of radiological lesion and laterality) and histopathology of FCD did not affect DQ-IQ.

Conclusions: Our study suggests that seizure characteristics including higher seizure frequency pattern, a history of epileptic spasm, status epilepticus, seizure clustering and early onset of seizure are risk factors of cognitive impairment in FCD patients.

Keywords: Pediatric epilepsy; Focal cortical dysplasia; Cognitive impairment; Risk factors

1. Introduction

Pediatric patients with uncontrolled epilepsy have been reported to be at risk of intellectual disability [1,2]. Epileptic seizures in patients with cortical dysplasia tend to be drug-resistant, resulting in concomitant cognitive impairment (epileptic encephalopathy) [3–5]. In cortical dysplasia, factors affecting cognitive function include early onset of seizure [6,7], prolonged-disease duration [3,8], large lesions [9] and histopathology of cortical dysplasia [4,10]. Although seizure frequency is also a risk factor [4,8]. Seizure frequency may fluctuate,

* Corresponding author at: National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorder, 886 Urushiyama, Aoi-ku, Shizuoka 420-8688, Japan.
E-mail address: kimura-n@umin.org (N. Kimura).

https://doi.org/10.1016/j.braindev.2018.07.014
0387-7604/

and transient seizure-free periods may be seen in the course of epilepsy. Even if seizures occur early during the course of epilepsy or the disease duration is prolonged, patients with low seizure frequency are typically not likely to develop cognitive impairment. Therefore, it is necessary to investigate the influence of seizure frequency on cognitive function in detail. In epilepsy patients, seizure type [11,12] and status epilepticus [13,14] also affect cognitive levels. However, there are few reports on the effect of seizure characteristics including seizure frequency with fluctuation, seizure type and status epilepticus on cognitive function in patients with a diagnosis of focal cortical dysplasia (FCD) confirmed by histological examination after epilepsy surgery.

We studied patients with FCD, which is the most common cause of medically refractory epilepsy, and analyzed mainly seizure characteristics as risk factors of cognitive impairment.

2. Material and methods

2.1. Inclusion of patients

We retrospectively evaluated the medical records of 813 patients who underwent epilepsy surgery at the National Epilepsy Center between 1985 and 2008, and included 77 patients with a diagnosis of FCD confirmed by histopathology (Table 1).

Histopathological findings in FCD were classified according to Palmini's classification [15].

Table 1
Clinical manifestation of 77 patients with focal cortical dysplasia.

	No. of patients (Total no. = 77)	%
Gender		
Boys or men	46	59.7
Girls or women	31	40.3
Febrile seizure	16	20.8
Age at seizure onset (years)		
0	12	15.6
1–2	16	20.8
3–4	17	22.0
5–9	21	27.3
15>	11	14.3
Disease duration until surgery (years)		
<2	1	1.3
2–4	10	13.0
5–9	17	22.0
10–19	27	35.1
≥20	22	28.6
Age at pre-surgical cognitive evaluation (years)		
<5	9	11.7
5–15	17	22.0
16–24	25	32.5
≥25	26	33.8
Distribution of DQ-IQ levels		
≤34	8	10.4
35–49	8	10.4
50–69	25	32.5
70–79	14	18.2
≥80	22	28.5
Pattern of seizure frequency*		
≥5 daily - daily	9	11.7
Daily-weekly	26	33.8
Daily-weekly (with transient seizure-free)**	19	24.7
Weekly-monthly	23	29.9
Habitual seizure types		
Focal impaired awareness seizure	46	59.7
Focal impaired awareness seizure + generalized Tonic clonic seizure	23	29.9
Focal aware seizure	4	5.2
Epileptc spasm***	4	5.2
Status epilepticus	10	13.0
Seizure clustering	53	68.8
MRI positive	70	90.9
FCD site		
Frontal lobe	52	67.5
Temporal lobe	10	13.0
Parietal lobe	1	1.3
Occipital lobe	7	9.1
Multilobe	7	9.1
Frontotemporal	1	14.2
Temporooccipital	4	57.1
Temporoparietoccipital	2	28.6
Laterality of FCD		
Left	36	46.8
Right	41	53.2
Histopathology of FCD (Palimi's classification)		
IA	1	1.3
IB	8	10.4
IIA	23	29.9
IIB	45	58.4
AEDs exposed until surgery		
Carbamazepine	53	68.8
Phenytoin	53	68.8
Phenobarbital	33	42.9
Clobazam	18	23.4
Valproate	13	16.9
Zonisamide	7	9.1
Clorazepate	5	6.5
Clonazepam	1	1.3
Nitrazepam	1	1.3
Primidone	1	1.3
Acetazolamide	1	1.3
Sulthiame	1	1.3
Number of AEDs around surgery		
1 AED	9	11.7
2 AEDs	34	44.2
3 AEDs	29	37.6
4 AEDs	4	5.2
5 AEDs	1	1.3

Abbreviations:
FCD = focal cortical dysphasia
AED = antiepileptic drug

* Refer to Fig. 1.
** Transient seizure-free: seizure-free periods longer than six months.
*** Epileptic spasm: patients with a history of epileptic spasms.

2.2. Factors for evaluation

We investigated the relationship between the developmental quotient or intelligence quotient (DQ-IQ) and clinical factors affecting DQ-IQ to reveal risk factors of cognitive dysfunction. DQ-IQ was evaluated just before surgery. As possible risk factors, we selected seizure characteristics including seizure frequency, seizure type, status epilepticus and seizure clustering, age at seizure onset, duration of epileptic seizures, location of FCD (FCD site, extent of radiological lesion and laterality) and histopathology of FCD.

2.3. Definitions and classification of groups for evaluation

2.3.1. Seizure frequency

Seizure frequency of "≥5 daily" was defined as five or more times a day, "daily" as one to four times a day, "weekly" as one to six times a week, and "monthly" as one to three times a month. Transient seizure-free period was defined as seizure control for more than six months.

Group classification by evolution of seizure frequency are shown in Fig. 1. Very high frequency pattern was defined as seizure frequencies fluctuating between ≥5 daily and daily for over two years. High frequency pattern was defined as seizure frequencies fluctuating between daily to weekly. Moderate frequency pattern was defined as seizure frequencies fluctuating between daily and weekly with transient seizure-free period. Low frequency pattern was defined as seizure frequencies fluctuating between weekly and monthly.

2.3.2. Habitual seizure types

Patients were classified by habitual seizure type (Table 1) into a group with only focal impaired awareness seizure (FIAS) (FAIS group), a group with generalized tonic clonic seizure (GTCS) in addition to FAIS (FAIS + GTCS group), a group with focal aware seizure (FAS) (FAS group), and a group with a history of epileptic spasm (ES group).

Epileptic spasms are defined by clinical manifestation of sudden flexion of extremities in clusters, in dependent of interictal epileptiform discharges corresponding to FCD site.

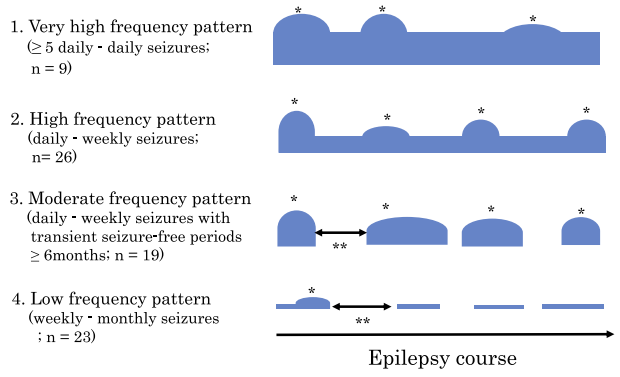

Fig. 1. Group classification by evolution of seizure frequency. *1: Seizure clustering. ** Transient seizure-free periods ≥6 months.

2.3.3. Status epilepticus and seizure clustering

Patients who had at least one seizure lasting more than thirty minutes in their seizure history were classified in the status epilepticus group. Patients who had at least one seizure clustering episode with three or more seizures in an hour in their seizure history were classified in the seizure clustering group.

2.4. Pre-surgical evaluation

All patients underwent pre-surgical evaluations including surface electroencephalography (EEG)-video monitoring, brain magnetic resonance imaging, computed tomography, and single-photon emission computed tomography.

Cognitive function was assessed by neuropsychologists to assess DQ-IQ before surgical intervention. The psychological tests were selected according to the developmental level and chronological age of patients. Seven patients were assessed with the Mother-Child-Counseling baby test [16], 13 patients with the Tanaka-Binet scale of intelligence [17], five patients with the Wechsler intelligence Scale for Children Revised, six patients with the Wechsler intelligence Scale for Children third edition, 44 patients with the Wechsler Adult Intelligence Scale Revised and two patients with the Wechsler Adult Intelligence Scale third edition. Cognitive dysfunction was classified by DQ-IQ level as follows: severe; <35, moderate; 35–49, mild; 50–69, borderline; 70–79, and normal; ≥80.

2.5. Statistics

Data were analyzed using SPSS version 23.0 (SPSS Inc, Chicago, IL, USA). Graphs were generated by SPSS or GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). Shapiro-Wilk test was used to test whether data were normally distributed. Welch's test was used to analyze variables that had normal distribution, while Mann-Whitney test was used to analyze variables that were not normal distributed.

Correlation was evaluated by regression analysis. Multivariate analysis was conducted by stepwise multiple regression analysis. Fisher's exact test or chi-square test was used to evaluate clinical manifestation or cognitive levels. A p value <0.05 was regarded as statistically significant. Group data are presented as mean ± standard deviation unless otherwise stated.

3. Results

3.1. Clinical manifestations of patients at pre-surgical evaluation

The clinical profiles of the 77 patients are shown in Table 1. The age at seizure onset was 5.0 ± 4.2 years (mean ± SD) (range: 14 days – 14 years) and all patients had childhood seizure onset. Mean disease duration until surgery was 14.5 ± 8.5 years (range: 7 months – 33 years). All but one patients had epilepsy for more than two years, and 66 patients (85.7%) had epilepsy for five years or longer. The age at evaluation of mean DQ-IQ just before surgery was 34.8 ± 10.7 years (range: 18 months – 36 years). The mean DQ-IQ was 60.5 ± 20.5 (range: 8–105) and 41 of 77 (53.2%) patients had mental retardation (DQ-IQ < 70).

3.2. Classification by seizure frequency pattern and DQ-IQ

DQ-IQ (mean ± SD) was 29.9 ± 15.9 in patients with the very high frequency pattern, 59.7 ± 16.7 with high frequency pattern, 74.2 ± 12.8 with moderate frequency pattern and 79.0 ± 9.9 with low frequency pattern (Fig. 2). Mean DQ-IQ was significantly lower in patients with the very high frequency pattern than in those with high, moderate, and low frequency patterns (Welch test, $p < 0.0001$). Mean DQ-IQ was significantly lower in patients with high frequency pattern than in those with moderate (Welch test, $p = 0.003$) and low frequency patterns (Welch test, $p < 0.0001$). Even when seizure frequency was the same, patients with transient seizure-free period had less mental retardation.

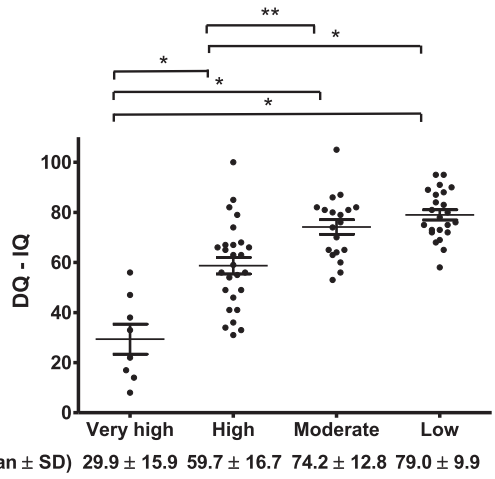

Fig. 2. Pattern of seizure frequency and DQ-IQ. Very high: seizure frequencies fluctuating between ≥5 daily and daily. High: seizure frequencies fluctuating between daily to weekly. Moderate: seizure frequencies fluctuating between daily and weekly with transient seizure-free period. Low: seizure frequencies fluctuating between weekly and monthly. * $p < 0.001$, ** $P = 0.003$, Welch test.

3.3. Classification by seizure type and DQ-IQ

Mean DQ-IQ was significantly lower in patients with a history of epileptic spasm than in those with FIAS (Welch test, $p < 0.001$), FIAS + GTCS ($p < 0.001$), or FAS ($p = 0.001$) (Fig. 3). Mean DQ-IQ in patients with FAS tended to be higher compared to patients with FIAS ($p = 0.051$) and was significantly higher compared to those with GTCS and FIAS ($p = 0.035$) in the course of epilepsy.

3.4. Classification by status epilepticus or seizure clustering and DQ-IQ

Mean DQ-IQ was significantly lower in patients with status epilepticus than in those without status epilepticus (Mann-Whitney test, $p = 0.004$) (Fig. 4-1). Mean DQ-IQ was significantly lower in patients with seizure clustering than in those without seizure clustering (Welch test, $p = 0.001$) (Fig. 4-2).

3.5. Age at seizure onset and DQ-IQ

In regression analysis, DQ-IQ in patients with younger seizure onset was lower compared to patients with older onset (regression analysis, $R^2 = 0.379$, $p < 0.001$) (Fig. 5).

3.6. Disease duration and DQ-IQ

There was no relation between disease duration and DQ-IQ in all patients. However we next analyzed the evolution of DQ-IQ over time after seizure onset by stratifying the patients by age of seizure onset, assuming that all patients did not have development delay at birth (Fig. 6). In all three subgroups with onset age <1 year,

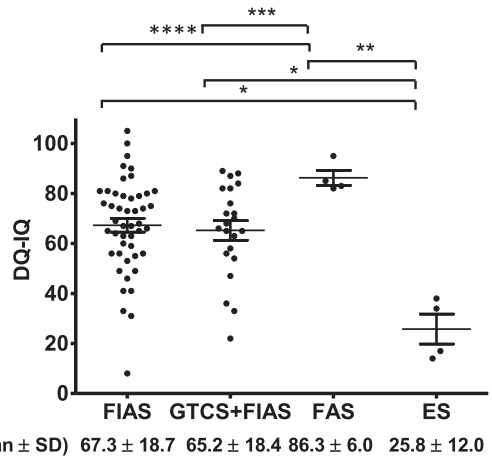

Fig. 3. Habitual seizure type and DQ-IQ. FIAS: focal impaired awareness seizure. GTCS: generalized tonic seizure. FAS: focal aware seizure. ES: epileptic spasm. * $p < 0.001$, ** $p = 0.001$, *** $p = 0.035$, **** $p = 0.051$, Welch test.

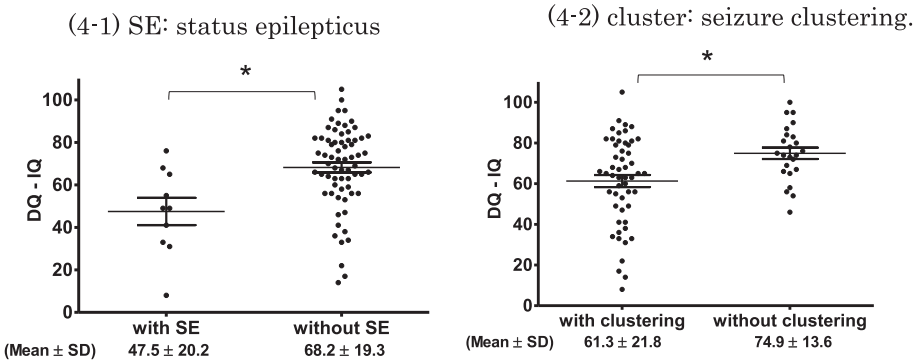

Fig. 4. Status epilepticus or seizure clustering and DQ-IQ. (4-1) SE: status epilepticus. * $p = 0.004$, Mann-Whitney test. (4-2) cluster: seizure clustering. * $p = 0.001$, Welch test.

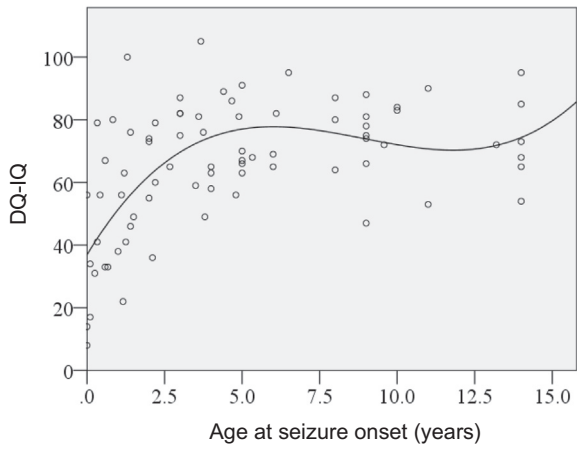

Fig. 5. Relations between age at seizure onset and DQ-IQ. A regression curve was applied to the data using SPSS, Regression analysis: $R^2 = 0.379$, $p < 0.001$.

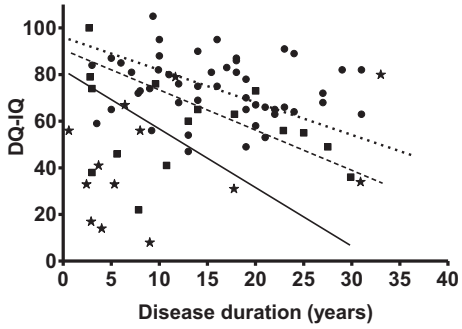

Fig. 6. Disease duration and DQ-IQ. Solid line (regression line) and stars denote patients with infantile onset of seizure; regression analysis: $Y = 2.5\ X + 80.4$, $R^2 = 0.281$, $p = 0.007$. Dashed line (regression line) and square denote patients with seizure onset at 1–3 years of age; regression analysis, $Y = -1.6\ X + 91.1$, $R^2 = 0.451$, $p < 0.0001$. Dotted line (regression line) and circles denote patients with seizure onset at 3 years of age or older; regression analysis: $Y = -1.2\ X + 96.9$, $R^2 = 0.543$, $p < 0.0001$.

1–3 years and >3 years, there was a significant relationship between disease duration and DQ-IQ, and patients with earlier seizure onset showed faster decline of DQ-IQ.

3.7. Location of FCD, extent of radiological lesion, histopathology and DQ-IQ

Mean DQ-IQ was 66.6 ± 17.8 in patients with FCD in the frontal lobe, 71.9 ± 10.5 in the temporal lobe, 87.0 in the parietal lobe, 66.7 ± 24.3 in the occipital lobe and 44.0 ± 34.1 in multiple lobes with extensive radiological lesions. There were no significant differences in DQ-IQ among various locations and among different degrees of radiological FCD. Mean DQ-IQ in patients with FCD in multiple lobes tended to be lower than that in temporal lobe ($p = 0.075$). Mean DQ-IQ also did not differ between patients with FCD in the left hemisphere and those in the right hemisphere (67.3 ± 18.8 vs. 64.0 ± 22.2). Mean DQ-IQ was 61.6 ± 22.3 in patients with FCD type IB, 65.3 ± 18.9 in type IIA and 66.6 ± 21.5 in type IIB. There was no significant difference in DQ-IQ among the three types of FCD.

4. Risk factors of mental retardation in multiple regression analysis

A stepwise multiple regression analysis was conducted to estimate the clinical factors that affect presurgical DQ-IQ. High seizure frequency pattern, a history of epileptic spasm and presence of status epilepticus were significant risk factors of DQ-IQ decline, while FAS decreased the risk [$F\ (4,\ 72) = 30.88$, $R^2 = 0.63$, $p < 0.001$] (Table 2). Higher seizure frequency pattern was the most important factor affecting DQ-IQ. The linear regression equation is as follows: DQ-IQ = 38.28 + (10.97 × pattern of seizure frequency) − (23.50 × epileptic spasm) + (15.07 × FAS) − (17.10 × status epilepticus).

5. Discussion

We investigated the factors related to cognitive function in childhood onset FCD patients. Aggravating factors for DQ-IQ were early onset of seizures, higher

Table 2
Multiple regression analysis for clinical factors affecting DQ-IQ at presurgical evaluation.

	Unstandardized Coefficients	Standardized Coefficients	Significance	95% Confidence interval	
				Lower bound	Upper bound
(Constant)	38.28			28.56	48.00
Seizure frequency pattern (1: Very high, 2: high, 3: moderate, 4: low)	10.97	0.55	<0.001	7.80	14.14
A history of epileptic spasm	–23.50	−0.26	0.002	−37.95	−9.04
Focal aware seizure	15.07	0.16	0.026	1.90	28.24
Status epilepticus	−17.10	−0.28	<0.001	−25.95	−8.26

F (4, 72) = 30.88, R2 = 0.63, $p < 0.001$.

seizure frequency pattern, a history of epileptic spasm and presence of status epilepticus. On the other hand, habitual FAS and seizure-free period up to 6 months in the course of epilepsy seem to decrease the risk of cognitive impairment.

5.1. Seizure frequency on DQ-IQ.

Clinical findings of patients stratified by DQ-IQ level are shown in Table 3. The largest proportion of patients with very high seizure pattern had DQ-IQ < 35 ($p < 0.05$ versus DQ-IQ 35–49 and versus DQ-IQ ≥ 50 groups). Conversely, the majority of patients with low seizure frequency pattern had DQ-IQ ≥ 80 ($p < 0.05$ versus DQ-IQ < 70 groups). Therefore, seizure frequency pattern was important factors affecting cognitive development. The frequency of FCD patients with transient seizure-free period has been reported to be 16.7% [18] and was 24.7% in our study. Frequent or continuous seizures may lead to inadequate recovery from dendritic injury, resulting in retardation [19,20]. These data suggest that transient seizure control by antiepileptic drugs may ameliorate mental retardation.

5.2. Habitual seizure type and DQ-IQ

In our study, epileptic spasms were found in four of 77 patients (5.2%). These four patients showed profound cognitive impairment (DQ-IQ 14–38), and had DQ-IQ < 35 ($p < 0.05$) (Table 3). Some studies found epileptic spasm in 17.5–21.6% of FCD patients [4,18] and those patients had severe to moderate mental retardation [3,21]. On the other hand, four patients with habitual FAS in our study had normal DQ-IQ levels (Fig. 3). Several studies showed that in temporal lobe epilepsy, seizure activity during FAS was confined to ipsilateral

Table 3
Number of patients in each category of DQ-IQ levels.

DQ-IQ levels	<35	35–49	50–69	70–79	≥80
Seizure frequency pattern					
1. Very high (%)	6 (75.0)[a]	2 (25.0)	1 (4.0)	0	0
2. High (%)	2 (25.0)	6 (75.0)	13 (52.0)	2 (14.2)	3 (13.6)
3. Moderate (%)	0	0	7 (28.0)	4 (28.6)	8 (36.4)
4. Low (%)	0	0	4 (16.0)	8 (57.0)	11 (50.0)[e]
Seizure type					
1. Epileptic spasm (%)	3 (37.5)[b]	1 (12.5)	0	0	0
2. Focal aware seizure (%)	0	0	0	0	4 (18.2)
Status epilepticus (%)	3 (37.5)	3 (37.5)	3 (12.0)	1 (7.1)	0
Seizure clustering (%)	8 (100)	7 (87.5)	18 (72.0)	7 (50.0)	8 (36.4)
Age at seizure onset, range (years)	0.36 ± 0.41[c] (0–1.2)	2.5 ± 2.8 (0.33–14)	5.3 ± 5.1 (0–14)	6.0 ± 2.7 (0.33–14)	6.5 ± 6.8 (0.83–14)
Infantile onset (%)	7 [d] (87.5)	1 (12.5)	3 (12.0)	1 (7.1)	1 (4.5)
Disease duration, range (years)	10.0 ± 9.8 (2.4–30.9)	14.1 ± 10.5 (3.2–29.9)	16.6 ± 5.1 (0.58–31.0)	12.8 ± 2.7 (0.33–27.0)	15.0 ± 6.8 (0.83–33.0)
No. of patients	8	8	25	14	22

a) Among patients with very high seizure frequency, significantly higher percentage was in DQ-IQ < 35 group than in DQ-IQ 35–49 group (Fisher's exact test, $p = 0.066$) or DQ-IQ ≥ 50 groups ($p < 0.0001$). b) Among patients with epileptic spasm, significantly higher percentage was in DQ-IQ < 35 group than in the other groups (Fisher's exact test, $p < 0.05$). c) Age at seizure onset was significantly younger in DQ-IQ < 35 group than in the other groups (Mann-Whitney test, $p < 0.01$). d) Among patients with infantile onset of seizure, significantly higher percentage was in DQ-IQ < 35 group (Fisher's exact test, $p < 0.05$). e) Among patients with low seizure frequency, significantly higher percentage was in DQ-IQ ≥ 80 group than in DQ-IQ < 70 groups (Fisher's exact test, $p < 0.05$).

temporal lobe, but seizure activity during FIAS spread to bilateral frontoparietal neocortices and midline subcortical structures thereby disrupting neocortical function [22,23]. Therefore, FAS may result in much less brain damage than FIAS.

Status epilepticus was reported to be present in 7.5 to 15.8% of patients with FCD [4,18] and was found in ten patients (13.0%) in our study. Status epilepticus causes brain and hippocampus damage [13,14,24]. Brief seizures lasting <5 min triggered neuronal damage that recovered completely, but severe seizures such as status epilepticus and clusters induced persistent dendritic injury in animal models [25].

5.3. Age at onset and DQ-IQ

In our study, the majority of patients with infantile onset of seizure had DQ-IQ < 35 ($p < 0.05$) (Table 3), consistent with some previous reports [3,5]. FCD patients with infantile onset of seizure may have highly frequent seizures resulting in severe cognitive impairment. Patients with infantile onset of seizure should be evaluated for indication of surgical intervention [26,27].

5.4. Disease duration and DQ-IQ

Disease duration has been reported to be associated with cognitive deficits [3,8]. In this study, there was no relation between disease duration and DQ-IQ in all patients. The reason is that the majority of the subjects had prolonged seizure duration (over 10 years in 67.3%) and very few had short seizure duration (<2 years in only 1 patient). This may have biased the analysis. Therefore, this finding has to be interpreted with caution. Moreover, when patients were stratified by age of onset, simulated evolution of DQ-IQ after onset of seizures showed that earlier seizure onset and prolonged disease duration contributed to the deterioration of DQ-IQ (Fig. 6). These results suggest that patients with prolonged disease duration and early onset of seizure tend to develop cognitive impairment.

5.5. Location of FCD, extent of radiological lesion, histopathology and DQ-IQ

In the present study, FCD site and laterality were not associated with DQ-IQ before surgery. In epilepsy patients, development of cognitive deficits is not associated with localized disruption at the site of epileptic foci, but is related to disruption of whole brain networks [28,29]. Previous studies have shown that patients with large lesions involving more than one lobe were more likely to have cognitive impairment [4,9] than patient with lesions involving only the frontal or temporal lobe [6], but we observed no decrease in DQ-IQ in patients with FCD involving multiple lobes. In previous studies, patients with FCD type I were more likely to manifest mental retardation than patients with FCD type II [4,5]. Our study showed no association between histopathology of FCD and cognitive deficits. This may be related to the small number of patients with FCD type I in our study.

5.6. Limitation

Since this study had a retrospective design, the same neuropsychological tests were not used in all subjects with a wide age range. Thus study was conducted in the tertiary epilepsy center, resulting in possible biased results by relatively longer latency from the onset to epilepsy surgery. Furthermore, we cannot exclude the possibility that antiepileptic drugs had adverse effects on cognitive development.

6. Conclusions

Our study suggests that seizure characteristics including higher seizure frequency pattern, a history of epileptic spasm, status epilepticus, seizure clustering and early onset of seizure are risk factors of cognitive impairment in FCD patients.

7. Disclosure of conflicts of interest

None of authors has any conflict of interest to disclose.

Acknowledgements

We thank Dr. Tadahiro Mihara who performed the surgeries from 1985, and the neuropsychologists at the National Epilepsy Center, Shizuoka. We would like to express our gratitude to the patients and their families for their cooperation.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Bourgeois BF, Prensky AL, Palkes HS, Talent BK, Busch SG. Intelligence in epilepsy: a prospective study in children. Ann Neurol. 1983;14:438–44.
[2] Ellenberg JH, Hirtz DG, Nelson KB. Do seizures in children cause intellectual deterioration? N Engl J Med. 1986;314:1085–8.
[3] Jonas R, Asarnow RF, LoPresti C, et al. Surgery for symptomatic infant-onset epileptic encephalopathy with and without infantile spasms. Neurology 2005;64:746–50.

[4] Krsek P, Pieper T, Karlmeier A, Hildebrandt M, et al. Different presurgical characteristics and seizure outcomes in children with focal cortical dysplasia type I or II. Epilepsia 2002;50:125–37.
[5] Lawson JA, Birchansky S, Pacheco E, et al. Distinct clinico-pathologic subtypes of cortical dysplasia of Taylor. Neurology 2005;64:55–61.
[6] Freitag H, Tuxhorn I. Cognitive function in preschool children after epilepsy surgery: rationale for early intervention. Epilepsia 2005;46:561–7.
[7] Vasconcellos E, Wyllie E, Sullivan S, et al. Mental retardation in pediatric candidates for epilepsy surgery: the role of early seizure onset. Epilepsia 2001;42:268–74.
[8] D'Argenzio L, Colonnelli MC, Harrison S, et al. Cognitive outcome after extratemporal epilepsy surgery in childhood. Epilepsia 2011;52:1966–72.
[9] Klein B, Levin BE, Duchowny MS, Llabre MM, et al. Cognitive outcome of children with epilepsy and malformations of cortical development. Neurology 2000;55:230–5.
[10] Widdess-Walsh P, Kellinghaus C, Jeha L, et al. Electro-clinical and imaging characteristics of focal cortical dysplasia: correlation with pathological subtypes. Epilepsy Res. 2005;67:25–33.
[11] Bowley C, Kerr M. Epilepsy and intellectual disability. J Intellect Disabil Res. 2000;44:529–43.
[12] Farwell JR, Dodrill CB, Batzel LW. Neuropsychological abilities of children with epilepsy. Epilepsia 1985;26:395–400.
[13] Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006;5:246–56.
[14] Wong M, Guo D. Dendritic spine pathology in epilepsy: cause or consequence? Neuroscience 2013;251:141–50.
[15] Palmini A, Najm I, Avanzini G, et al. Terminology and classification of the cortical dysplasias. Neurology 2004;62:S2–8.
[16] Koga Y. Mother-Child-Counseling baby test. Tokyo: Doubun Shoin, (in Japanese) 1967.
[17] Tanaka H. Tanaka-Binet scale of intelligence. Tokyo: Taken Shuppan. (in Japanese) 1987.
[18] Fauser S, Huppertz HJ, Bast T, et al. Clinical characteristics in focal cortical dysplasia: a retrospective evaluation in a series of 120 patients. Brain 2006;129:1907–16.
[19] Swann JW, Al-Noori S, Jiang M, Lee CL. Spine loss and other dendritic abnormalities in epilepsy. Hippocampus 2000;10:617–25.
[20] Wong M. Modulation of dendritic spines in epilepsy: cellular mechanisms and functional implications. Epilepsy Behav. 2005;7:569–77.
[21] Asarnow RF, LoPresti C, Guthrie D, et al. Developmental outcomes in children receiving resection surgery for medically intractable infantile spasms. Dev Med Child Neurol. 1997;39:430–40.
[22] Englot DJ, Yang L, Hamid H, et al. Impaired consciousness in temporal lobe seizures: role of cortical slow activity. Brain 2010;133:3764–77.
[23] Blumenfeld H, Jackson GD. Should consciousness be included in the classification of focal (partial) seizures? Epilepsia 2013;54:1125–30.
[24] Tsuchida TN, Barkovich AJ, Bollen AW, Hart AP, Ferriero DM. Childhood status epilepticus and excitotoxic neuronal injury. Pediatr Neurol. 2007;36:253–7.
[25] Guo D, Arnspiger S, Rensing NR, Wong M. Brief seizures cause dendritic injury. Neurobiol Dis. 2012;45:348–55.
[26] Kimura N, Takahashi Y, Shigematsu H, et al. Developmental outcome after surgery in focal cortical dysplasia patients with early-onset epilepsy. Epilepsy Res. 2014;108:1845–52.
[27] Loddenkemper T, Holland KD, Stanford LD, et al. Developmental outcome after epilepsy surgery in infancy. Pediatrics 2007;119:930–5.
[28] Vlooswijk MC, Vaessen MJ, Jansen JF, et al. Loss of network efficiency associated with cognitive decline in chronic epilepsy. Neurology 2011;77:938–44.
[29] Waites AB, Briellmann RS, Saling MM, Abbott DF, Jackson GD. Functional connectivity networks are disrupted in left temporal lobe epilepsy. Ann Neurol. 2006;59:335–43.